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The Peanut Allergic Patient: Diagnosis, Treatment, and Prevention

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ABSTRACT

The Peanut Allergic Patient: Diagnosis, Treatment, and Prevention

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The prevalence of peanut allergies (PAs) continues to rise through recent decades, despite the best attempts to reverse that trend. PAs are unpredictable and can be life-threatening. Therefore, it is imperative that nurse practitioners (NPs) are fully aware of the most recent guidelines and evidence regarding diagnosis, treatment, and prevention of PAs. This article presents information on current research in diagnosis and treatment of PA, as well as the latest guidelines established to prevent PA development. NPs should understand this information, allowing them to provide the best care possible for their patients.

Keywords: peanut, hypersensitivity, treatment, diagnosis, allergy, prevention, immunotherapy, guidelines

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In 2013, an eleven year-old boy, living in the Western United States, went to a friend's house to play. While visiting, he was offered a snack, a pretzel filled with peanut butter. After realizing what he had bitten into, he immediately spat it out, knowing that he was severely allergic to peanuts. His mother was notified and rushed to his aid with an epinephrine injection. Unfortunately, her response was too late. This boy passed away from an anaphylactic reaction to peanuts resulting in cardiac arrest.[1]

Sadly, lethal situations like this one occur periodically as peanut allergies (PAs) become more prevalent. In fact, self-reported PAs in the United States (U.S.) increased by more than three-fold from 0.4% in 1997 to 1.4% in 2008,[2] with similar increasing prevalence found in Canada, the United Kingdom (UK), and Australia.[3-5] More recently, a 2014 Massachusetts cohort was tested for PA, and PA proportion in their sample was 4.9%. .[6]

PA typically develops in the first few years of life. However, PA is not strictly a pediatric issue as many live with PAs throughout their lives. Approximately 20% of those diagnosed with PAs go into remission without treatment, or "outgrow" their allergy, by five years of age.[7,8] Remission rates for PAs are much lower than remission rates of allergies to egg and cow's milk, 80% and 85% respectively.[7] The probability of PA remission decreases by half for participants who have skin prick tests (SPTs) >6mm and/or peanut specific IgE levels >3 KUA/L before 2 years of age.[8] Similarly, PA patients, age 4 to 20 years, with initial IgE levels greater than 10 KUA/L are unlikely to gain remission.[7] An increase of 3mm or greater in SPT between ages 1 and 4 years predicts that PA will persist, but decreases in SPT predicts remission.[8]

Being diagnosed with PA is life-changing and can be frightening as one realizes it can be life-threatening. Consequently, PA not only alters what one eats, it creates anxiety in day-to-day

living for people who are allergic and their families and friends.[9] Efforts to manage PAs focus on increasing awareness of PAs and creating peanut-free environments in some schools.[10] Additionally, some countries require that pre-packaged food labels indicate any possibility of the product containing peanuts or any chance of cross-contamination. These labels can be overly cautious as some companies include the possibility of peanut cross-contamination to protect consumers from inadvertent exposures and themselves from liability.[11] In the UK, 69% of cereals and 56% of confectionary items are labeled with traces of nuts, but nuts are not included in the ingredient list.[11] Despite strategies to cope with PAs and minimize exposure, a risk of accidental exposure remains.

Avoidance has been the only recommendation over the past several decades.[12] Fortunately, recent studies on PA treatment show promise in the effectiveness and safety of oral immunotherapy (OIT) and sublingual immunotherapy (SLIT).[13-15] Additionally, recently improved diagnostic testing provides more accurate results while minimizing patients' risk.[16]

Due to the increasing PA prevalence,[6] nurse practitioners (NPs) need to understand how to effectively care for patients with PA. By better understanding PA development, available tests and treatments, and the associated risks, NPs can provide education needed for appropriate management and assist patients with PA to better live with their allergy.

The purpose of this clinical feature is to present what NPs need to know about their role in the care of PA patients. Specifically, it includes an overview of PA development, typical history and physical examination findings, the latest research on effective diagnostic and treatment techniques, the latest guidelines on preventing PAs, and tips for teaching patients and families.

Development of Peanut Allergy

Understanding how allergies develop may reveal a pathway to prevention. Several theories attempt to explain PA development, yet the exact cause remains unknown and is likely due to a combination of factors. Theories include the hygiene hypothesis,[17] maternal-fetal pathway,[18] external exposure,[19] and the dietary hypothesis.[17]

The hygiene hypothesis implies that minimizing exposure to harmful organisms inadvertently weakens the immune system. Specifically, improved sanitation has eliminated or minimized exposure to bacteria and viruses, which previously strengthened immune systems. Without these exposures, people become more likely to react against non-harmful agents[17] like peanuts.

The maternal-fetal pathway hypothesizes initial exposure to peanuts occurs in utero and/or through breastfeeding. Infants as young as four-months old have tested positive to peanuts with SPT, suggesting first exposure and sensitization occurred either in utero and/or through breast milk.[18] In contrast, a 2014 study found that maternal ingestion of highly allergenic foods in early trimesters provides protection against allergy in mid-childhood.[6]

According to the external exposure theory, exposure occurs through inhalation or compromised skin, such as eczema,.[19] During an eczema flare-up, the body initiates its defense system—inflammation. If exposure to peanuts occurs at the compromised site, then the immune system might inadvertently identify peanuts as the offending agent and react in subsequent exposures. In fact, research in mice suggests hypersensitivity to peanuts is developed through cutaneous or environmental exposure,[12] but tolerance is developed through oral exposure.[12,20]

The dietary hypothesis is based on differences between the Western and Mediterranean diets. Compared to the typical Western diet, the Mediterranean diet provides broader exposure to

various foods, including peanuts, which theoretically helps the immune system recognize what is harmful and what is not.[17] For example, Jewish children in Israel consumed peanut products at an earlier age than their UK counterparts. The PA rate was ten times higher for children in the UK than children in Israel.[21] The dietary hypothesis is consistent with current guidelines for introducing peanuts into infants' diet.[22]

Clinical Presentation

History of Present Illness

The integumentary, cardiopulmonary, and gastrointestinal systems are most commonly affected with food allergies.[12] Therefore, patients with PA typically present with a history consistent with allergic reactions, including complaints of itching; rashes; hives; swelling; wheezing; coughing; voice changes; or gastrointestinal issues, including nausea, vomiting, and diarrhea. In addition to identifying symptoms, the timing of symptoms after ingestion is also important. PA is a type 1 IgE mediated response, and symptoms occur rapidly after exposure, usually only minutes later.[18,19] The amount of peanut consumed may likely determine the severity of reaction.[19] Other co-factors that can influence reactions or reduce the reaction threshold include recent exercise, current medications, and comorbid conditions.[12,16]

Past Medical and Family History

Patients with a family history of PA and/or concurrent diagnosis of eczema or asthma are at increased risk for developing PA. Eczema, asthma, and food allergies are often concurrently diagnosed because of an atopic gene.[12] PAs develop in 25-30% of patients with a strong atopic history.[16] Similarly, 90% of people with PA will have a history of eczema, asthma, rhinitis, or allergy to other foods.[19] Thus, NPs should ask about these conditions or symptoms in patients and family members. A concurrent diagnosis of PA and asthma, particularly if undertreated, is

concerning because this combination increases the risk of anaphylactic reaction.[19] Additionally, patients with asthma have an increased likelihood of a severe reaction during oral peanut challenges.[23]

Physical Examination

Patient history should be the primary cause to suspect PA, because physical examination findings may be unremarkable at the time of evaluation. NPs should evaluate any system affected by the reaction, including integumentary, cardiopulmonary, and gastrointestinal, as mentioned above. History of present illness, past medical and family history, physical examination, and timing of reaction consistent with PA should trigger an NP to order diagnostic testing or refer to a specialist.

Diagnosis

Diagnostic tools include oral food challenges (OFC), skin prick testing (SPT), peanut specific serum (sIgE) and component IgE testing. No one diagnostic test is perfect.[24] Using them in combination will provide more accurate information than any one test alone. Additionally, PA testing should be limited to patients with a history of symptoms, because positive results can occur in both SPT and sIgE in people without a history of symptoms.[16] Positive SPT and/or sIgE results without a history of symptoms, or peanut-sensitization, does not always indicate PA. In fact, the majority of the population who are peanut-sensitized do not have an allergy.[16] However, early accurate diagnosis is imperative as anaphylaxis is more common in PAs than other foodborne allergies.[25]

Oral Food Challenge

Physician-supervised OFC is the "Gold Standard" for PA testing because it is the most definitive test available,[16] but it has flaws. OFC is simple but can be time-consuming and

potentially dangerous. A risk of reaction is present when introducing a potential allergen, and reaction severity is unpredictable[23,26] with anaphylaxis being the greatest risk. Any patient with a recent history of anaphylaxis should not be tested using OFC.[12] OFCs are supervised by a physician, typically an allergist. Patients are given peanut product orally and monitored for signs of allergic reaction. Emergency supplies and medications are available in case a severe reaction develops. NPs should be familiar with OFCs and the risks involved and educate their patients accordingly.[16]

Skin Prick Testing

SPT is less risky but not as accurate as an OFC and is typically done by specialists.[27] SPTs introduce a small amount of antigen into the tissue via skin prick. After 15 minutes the allergen prick site is compared to a control prick site and assessed for the development of hives, indicating a reaction. Typically a wheal ≥3mm is considered indicative of PA, but only if paired with a positive history suggesting PA.[19] However, some studies used wheals of >4mm[28] and ≥8mm[27] to diagnose PA, even without a positive history. Limitations of SPT for PA include low specificity (30%), variability in concentration of test reagents, pressure applied when pricking the skin, location placed, and timing of reading results.[16]

Peanut Specific Serum IgE

sIgE testing measures the amount of peanut-specific IgE in the patient's serum. Elevated levels correlate with an increased likelihood of allergy. Sicherer and Wood found sIgE concentrations above 15 kU_A/L had more than a 95% chance of clinical reactivity.[16] However, Dang et al. found sIgE had a high specificity (98%), but low sensitivity (26%) when using the cutoff of 15 kU_A/L to diagnose PAs with a positive predictive value (PPV) of 95%.[27] Sensitivity refers to the likelihood of a positive result if actually positive, and specificity refers to likelihood

of a negative result if negative. Therefore, a low specificity means there is an increased risk of false-negative results. sIgE testing can be completed in a primary care clinic but requires access to a lab capable of running this test. Correct test ordering and interpretation can be complex. The NP unfamiliar with these tests should refer the patient to an allergist to ensure proper testing and interpretation.[19]

Component IgE Testing

Component testing is another blood test that can be completed in a primary care clinic.[27] IgE levels are measured for each of the identified peanut protein components. The components are labeled Ara h1-11, and each has different properties that correlate to an allergic response. For example, Ara h2 has an increased correlation with reactivity and severity. Furthermore, if IgE binds to Ara h2 along with either Ara h1 or 3, then severe reactions are more common. However, Ara h8 is not related to a strong reaction, but indicates cross-reactivity with birch.[24] Similarly, Ara h1, 2, and 3 were more often positive in subjects who failed OFC, and Ara h8 was more frequently positive in people who passed OFC.[24] Specifically Ara h2 was more sensitive and specific for peanut allergy than Ara h1, 3, 8, or IgE testing.[24] Despite these results, studies have not directly correlated the binding of Ara h2 to severe reactions.[16] Dang et al. found component testing is more accurate than either SPTs or sIgE in determining PA.[27] In this study, participants first underwent SPTs and OFCs to determine allergy status and then completed sIgE and component testing for Ara h2. Results were then compared to OFCs to determine testing accuracy. Sensitivity for component testing (60%) is much higher than sIgE (26%) when compared using the same specificity (98%) (CI 95%; $P < .001$).[27] Component testing accurately diagnosed more patients than either SPT or sIgE. If component testing were used as a follow-up test to sIgE, it could minimize the need for OFCs by as much as two-thirds.[27]

Each testing modality has benefits and limitations. OFCs are still considered the gold standard but have risks of anaphylaxis.[16,27] SPTs are useful for quick results when history suggests PA.[27] OFCs and SPTs are typically done by specialists.[27] Conversely, Ara h2 and sIgE testing can be done in general practice clinics. Current recommendations suggest that if patient history is positive for allergic reaction, then SPT or sIgE may be sufficient. If these test results are not definitive, then OFC is required.[27] Patients without a history of allergic reaction should not be tested as it is costly and can cause undue burden on these patients.[16] NPs should know about available tests to educate patients and families.

Treatment

NPs should be aware of current treatment options to better educate patients. The initial treatment recommendation should be avoidance,[12] which can be very difficult.[15] Beyond that, any patient diagnosed with PA should be prescribed an EpiPen due to the risk of anaphylaxis.[12,23] Antihistamines are beneficial for treatment of acute mild reactions.[29] Recent advancements can help many patients develop tolerance to varying amounts of peanut. This progress in treatment will, hopefully, lead to complete desensitization, allowing worry-free peanut ingestion for those completing treatment.

Investigational Treatment Modalities

Two investigational options for treatment are SLIT and OIT. SLIT is administered by placing drops of peanut extract under the tongue, and OIT is administered through ingestion of the allergen, typically peanut powder. Both methods are relatively safe and effective in creating a level of tolerance to peanuts.[13-15] Either treatment option can benefit people who follow the care plan, but the treatments come with risks.

Administration of SLIT and OIT follow a similar protocol, beginning with an escalation phase followed by a maintenance phase. Therapy begins at low doses, and every one to two weeks the dose is increased under clinic supervision. The patient continues to take the safely consumed dose at home until the next increase. If an allergic reaction occurs, families treat as instructed and notify the clinic, dosing adjustments are made, and patients are again advanced as tolerated. Once the maintenance dose is reached, the patient continues on that same dose. The time frame for each phase varies from several weeks or months (escalation) to years (maintenance).[13,14,30]

Compared to OIT, doses for SLIT are much lower.[13,14,30] This is because sublingual administration results in systemic absorption three to ten times faster than oral administration.[31] Injection is the only route faster than sublingual, and injection has proven to be dangerous for peanut immunotherapy.[13,31]

With the use of lower doses in SLIT, adverse events (AEs) are less frequent compared to OIT. In a pilot study, AEs occurred in 9% of SLIT doses and 43% of OIT doses ($P < .001$).[14] Reactions in both groups were typically mild; however, moderate reactions and reactions requiring antihistamines, beta2-agonists, and epinephrine were more common in the OIT group. Additionally, intolerable symptoms in the OIT group led to more study withdrawals than the SLIT group. [14] Although this evidence suggests using SLIT over OIT, effectiveness needs to be considered. Participants in both groups experienced at least partial desensitization, but differences between the groups were significant. Participants in the OIT group developed improved desensitization, tolerating an average of 24 peanuts compared to an average of 1 or 2 peanuts in the SLIT group.[14]

Another treatment modality currently being studied is epicutaneous immunotherapy (EPIT). EPIT is administered through a patch placed on the skin. A recent study compared 2 different strengths, 100 and 250 mcg, against placebo.[32] Participants (n = 74) went through an escalation phase, much like SLIT and OIT, but this escalation focused on tolerance to the patch for longer time periods each day, thereby increasing the amount absorbed through longer exposure. Although the ongoing study is designed for 130 weeks, recent evaluation based on OFC results after 52 weeks indicated EPIT created greater tolerance to peanuts with both the 100 and 250mcg doses than placebo (P = .005 and P = .003, respectively).[32] The difference between the treatment groups was insignificant (P = .48). Treatment response was greater in participants younger than 11 years of age. EPIT appears relatively safe; there were no severe reactions. However, AEs were common, occurring in 79.8% of doses, but they were mild and generally limited to the patch site.[32]

SLIT, OIT and EPIT show promise in treating PAs, but studies are limited by small sample sizes,[13-15,30,32] high dropout rates,[14,30] and exclusion of subjects with history of anaphylaxis or other severe reactions.[14,30,32] Further study is needed.[13-15,30,32]

Management

Prevention

The devastating nature of PAs has encouraged research on PA prevention. Du Toit et al.'s study, Learning Early about Peanut Allergy (LEAP), found introducing peanut into the diet of high-risk infants in their first 11 months can reduce the risk of developing PA.[28] Infants (4-11 months old) who had severe eczema, egg allergy, or both were classified as high-risk and met inclusion criteria. Children were excluded if they were low risk (no history of egg allergy or severe eczema), or they had a SPT result for peanuts larger than 4 mm, because this increased

their likelihood of being allergic.[28] Participants were screened by SPT and then randomly assigned into either the peanut-consumption or peanut-avoidance group. Among participants with a negative SPT (0mm) at baseline, regular peanut consumption resulted in an 86.1% relative reduction in PA at 60 months of age with a PA prevalence of 13.7% in the avoidance group and 1.9% in the consumption group (95% CI, 3.4-20.3; $P < 0.001$).[28] Among participants with a positive SPT (<4mm) at baseline, regular peanut consumption resulted a 70% relative reduction in PA at 60 months of age with a PA prevalence of 35.3% in the avoidance group and 10.6% in the consumption group (95% CI, 4.9-43.3; $P = 0.004$).[28]

LEAP-ON was a follow-up study involving the same participants in the LEAP study and aimed to determine if early peanut consumption provided long-lasting tolerance. After completion of the LEAP study, the consumption group was asked to abstain from peanuts for 12 months, and the avoidance group continued avoiding peanuts.[33] After this 12-month period, the early peanut-consumption group had a significantly lower PA prevalence (4.8%) than the early peanut-avoidance group (18.6%) ($P <0.001$). Although three children in the consumption group became peanut allergic over the 12-month period, the prevalence difference at 60 months vs. 72 months was not statistically significant ($P = 0.25$). Thus, LEAP-ON showed a sustained benefit from early introduction of peanuts.[33]

Perkin et al.[34] evaluated which age is it best to introduce allergenic foods into an infant's diet. Inclusion criteria were being three-months old and strictly breastfeeding. Participants were divided into two groups: standard (6 months) and early (3 months) introduction. The foods included peanuts, cooked egg, cow's milk, sesame, whitefish, and wheat. The standard group began introduction to these foods at 6 months of age at the parents' discretion. The early group had baseline SPTs completed and, if positive, then OFCs were completed. Those with negative

SPT or OFC were instructed to continue with this introduction protocol: first cow's milk; then peanut, hen's egg, whitefish, and sesame, in any order; and finally wheat.[34] If SPT and OFC were positive for any of these foods, then participants avoided those foods and continued per protocol with all others. For peanuts, the early introduction group had a lower prevalence (0/310) of PAs compared to the standard introduction group (13/525) ($P = 0.003$) in the per-protocol-analysis.[34] However, in intention-to-treat-analysis, there was no statistical benefit in early introduction of these foods at 3 months compared to 6 months.[34]

Research has impacted practice guidelines. In fact, the LEAP study influenced the National Institute of Allergy and Infectious Diseases (NIAID) to develop an addendum (2017) to the "Guidelines for the Diagnosis and Management of Food Allergy in the United States" (2010).[22] The addendum recommends, when appropriate, early introduction of peanuts to prevent PA.[22] Furthermore, it specifies that products containing peanuts should be introduced between four and eleven months of age for most infants. The timing of introduction coincides well with introduction of solids into infants' diets. The guidelines' recommendations are for specific groups of varying risk levels for developing PA (Table 1).[22] Early introduction of peanuts to an infant's diet can minimize the risk of developing PA, but it does not eliminate the risk completely.[28] Current guidelines are essential for primary care providers to understand and implement to help reverse the trend of increasing PA.

Role of the NP

NPs have important roles in prevention, early identification and diagnosis of PAs, and proper education in developing an allergy plan. Additionally, NPs should help patients understand what to expect from the allergist and current treatment options.

At a minimum, an allergy plan (Table 2) should include the following: how to remain safe with PAs and how to best avoid exposure, how to identify allergic reactions and/or anaphylaxis, what to do in case of a reaction, how to treat, and when to refer to an allergist.[19] As mentioned previously, patients with suspected PA should be prescribed an EpiPen.[17] NPs should emphasize the possibility of a biphasic reaction, a secondary anaphylactic reaction that can occur up to 72 hours after resolution of initial reaction.[17] This is one reason why auto-injectors come in pairs,[17] as well as a back-up in case one pen is faulty. Whenever an Epipen is used, the patient should be transported to the nearest hospital for monitoring and further treatment.

Conclusion

PA prevalence has been increasing over recent decades, and the prevalence of NPs in healthcare has also increased. These two factors increase the likelihood that NPs will be involved in assessing and managing patients with PAs. Recent advancements in diagnosis, treatment, and prevention are important for all NPs to understand. This clinical feature has addressed those advancements and provided the most recent information for NPs to manage PAs. As NPs fulfill their role in prevention and early identification of PAs, their patients will be more capable of managing this life-altering condition.

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Table 1- National Institute of Allergy and Infectious Diseases' Addendum Guidelines for Early Peanut Introduction[22]

Risk level	Recommendations
Low (No eczema and no food allergies)	• Introduce peanuts freely into diet, according to age appropriate guidelines, family preferences, and cultural practices • Introduce peanuts at home[22]
Moderate (mild to moderate eczema)	• Introduce peanuts around 6 months of age, according to age appropriate guidelines, family preferences, and cultural practices • Introduce other solids before peanuts to ensure developmental capability • Introduce peanut at home or in-office[22]

High (severe eczema, egg allergy or both)	• Introduce age-appropriate peanut-containing foods at 4-6 months of age
	• Introduce other solids before peanuts to ensure developmental capability
	• Evaluate peanut sIgE, SPT, or both before introducing peanut into diet and follow recommendations based on results
	• sIgE done in PCP office, SPT with specialist
	  • sIgE < 0.35 kUA/L, introduce peanut into diet
	  • sIgE ≥ 0.35 kUA/L, refer to specialist
	  • SPT ≤ 2 mm, introduce peanut into diet
	  • SPT 3-7 mm, refer to specialist for OFC
	  • SPT ≥ 8 mm, avoid peanuts and refer to specialist[22]

Children with identified peanut allergy	• Strict avoidance • In homes with children with known PA, discuss risks and benefits of adding peanuts to a new infant's diet[22]

Table 2- Peanut Allergy Plan[19]

Remain Safe	• Avoid peanuts, including restaurants with environmental exposure[20] • Read/trust nutrition fact labels[20] • Notify school/friends/family[19,29] • Keep EpiPen available
Identify reactions/anaphylaxis	• Watch for itching, rashes, hives, or swelling following peanut exposure[12,19] • Anaphylaxis can include coughing, wheezing, fatigue, drop in BP, closing of airway, and loss of consciousness[19]
Treatment	• For mild reactions treat with antihistamine[29] • For severe reactions use EpiPen as directed and go to local emergency department[17] • Can use short-acting beta-agonist to help with symptoms after EpiPen administration if asthmatic[29]
Refer to specialist	• If unable to manage symptoms, or family would like further consultation • See SPT/sIgE results in table 1[22]